

A double-blind comparison of balsalazide, 6.75 g, and sulfasalazine, 3 g, as sole therapy in the management of ulcerative colitis

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Accepted for publication 23 August 2001

SUMMARY

Background: Sulfasalazine is accepted therapy for active ulcerative colitis, but side-effects and intolerance are common. Balsalazide is an azo-bonded pro-drug which also releases 5-aminosalicylic acid into the colon, but uses an inert carrier molecule.

Aim: To compare the safety and efficacy of sulfasalazine, 3 g, with balsalazide, 6.75 g, in the initial daily treatment of mild to moderate ulcerative colitis.

Methods: A randomized, multicentre, double-blind, parallel group study was performed, with a treatment duration of 8 weeks. Patients on previous maintenance treatment were excluded. The trial medication was the sole treatment for the colitis. Efficacy was assessed by

patient diaries, symptom assessment, sigmoidoscopic appearance and histology.

Results: Fifty patients were recruited: 26 allocated to the balsalazide group and 24 to the sulfasalazine group. More patients withdrew due to adverse events in the sulfasalazine group (nine patients vs. one patient in the balsalazide group, $P = 0.004$). Improvement occurred in both groups, with a tendency to a faster response with balsalazide. Of the patients taking balsalazide, 61% achieved clinical and sigmoidoscopic remission.

Conclusions: Balsalazide, 6.75 g, is effective as the sole treatment for patients with mild to moderately active ulcerative colitis, with significantly fewer withdrawals due to side-effects than in a similar group of patients taking sulfasalazine, 3 g.

INTRODUCTION

Sulfasalazine is an effective treatment for ulcerative colitis in the maintenance of remission and in acute active disease.^{1–4} A recent review concluded that sulfasalazine remains the drug of choice for most patients to induce remission in active ulcerative colitis.⁵ Many patients, however, are unable to tolerate the drug at high doses, as side-effects necessitating withdrawal or dose reduction are common (up to 45%).³ Orally administered sulfasalazine is largely unabsorbed in the small intestine and mostly passes into the colon, where

it is split by colonic bacterial azoreductase into sulfapyridine and 5-aminosalicylic acid (mesalazine). Most of the sulfapyridine is absorbed from the colon and is responsible for many of the sulfasalazine side-effects.⁶ The 5-aminosalicylic acid component is the therapeutic agent and is believed to work topically at the colonic mucosa.^{7, 8}

Oral 5-aminosalicylic acid is unstable in gastric acid and is rapidly absorbed from the small intestine. A number of delivery systems have been devised to deliver 5-aminosalicylic acid to the colonic mucosa, including pH-dependent coating, delayed-release microspheres and azo-bonding of two 5-aminosalicylic acid molecules to each other.⁹ None of these delivery mechanisms has proved to be entirely satisfactory, with small bowel absorption of 5-aminosalicylic acid, passage of intact

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capsules and diarrhoea being problems in some patients with ulcerative colitis.^{10, 11}

Balsalazide is a 5-aminosalicylic acid pro-drug, in which 5-aminosalicylic acid is linked via an azo-bond to 4-aminobenzoyl- β -alanine, an inert and biologically inactive carrier molecule.¹² Balsalazide releases 5-aminosalicylic acid into the colon by the action of bacterial azoreductase, in a manner similar to sulfasalazine. The inert nature of the carrier molecule, in contrast to sulfasalazine, may allow more patients to tolerate the treatment and higher doses of 5-aminosalicylic acid to be delivered to the colon. Published trials with balsalazide have shown it to be superior to mesalazine in the induction of remission,^{13–15} and as effective as sulfasalazine and mesalazine in the maintenance of remission.^{16, 17} Trial data comparing balsalazide to sulfasalazine in active disease are limited to the abstract reports of this and one other study.^{18, 19}

The aim of this study was to compare the safety and efficacy of balsalazide, 6.75 g daily (equivalent to 2.36 g of 5-aminosalicylic acid), with sulfasalazine, 3 g daily (equivalent to 1.15 g 5-aminosalicylic acid), in the initial treatment of mild to moderately active ulcerative colitis.

METHODS

Patient selection

Patients were recruited from three hospitals in northern England. Patients gave written informed consent and local research ethical committee approval was obtained. The study was conducted under a clinical trials certificate (approval number 0181/031). Adults with newly diagnosed or recently relapsed ulcerative colitis were included. Patients who had experienced a previous attack were eligible if they were not on maintenance treatment. The diagnosis of active ulcerative colitis was confirmed by the presence of friable or spontaneously bleeding mucosa at sigmoidoscopy, in conjunction with a negative stool culture. Patients with systemic upset indicating the need for treatment with corticosteroids were excluded. Patients who had been treated with corticosteroids, including topical use, azathioprine or any 5-aminosalicylic acid preparations over the preceding 2 months were excluded. Individuals with significant renal or hepatic disease, known intolerance to sulfasalazine and women who were or might become pregnant during the study were also excluded.

Study design

This was a randomized, multicentre, double-blind, parallel group study comparing balsalazide, 6.75 g/day, with sulfasalazine, 3 g/day, administered in three divided doses, in the treatment of acute ulcerative colitis. Patients were screened for eligibility and given placebo matching the trial treatments for the first 2 days of the study to establish the baseline bowel habit. Treatment for the next 2 days comprised balsalazide, 4.5 g daily, or sulfasalazine, 2 g daily, equivalent to two-thirds of the full daily dose. On day 5, treatment was increased to the full dose. Study drugs were prepared, packed and labelled by Biorex Laboratories Ltd, Enfield, Middlesex, UK, in identical gelatine capsules. The study was conducted prior to the introduction of the international code of Helsinki Good Clinical Practice. Patients were treated over 8 weeks and visited the study sites at weeks 0, 2, 4 and 8. At the first visit, written informed consent was taken and patient demographics and a history of ulcerative colitis were collected. At each visit, weight, pulse, general well-being, bowel frequency, the presence/absence of stool blood, changes in smoking habits, other drugs and side-effects were recorded. Patients were also given diaries within which to record stool frequency, consistency and the presence of blood and/or mucus. These diaries were also used to collect any ill effects that the patients experienced whilst on study medication. On entry and at the end of the study, laboratory biochemistry and haematology were performed. Sigmoidoscopy was performed at weeks 0, 4 and 8, with rectal biopsies for histology at weeks 0 and 8. At the end of the study, an overall assessment was made to determine whether the patient had achieved remission. Remission was defined as a stool frequency of two or less per day without blood and with a sigmoidoscopic appearance of normal rectal mucosa or minimal erythema.

All histology specimens were examined and graded for inflammation by one histopathologist blind to the treatment and stage of the study.

Statistical analysis

The sample size of 50 patients was calculated to have 80% power to detect a difference in intolerance, measured by withdrawals due to adverse events, of 35% (45% vs. 10%), at a significance level of 5%.²⁰

Demographic data and medical history were summarized by means and standard deviations or frequency tables as appropriate. Remission rates for each treatment were compared using a chi-squared test on the basis of an intention-to-treat analysis. Signs and symptoms were summarized by means and standard deviations or frequency tables as appropriate, and treatments were compared either by the two-sample *t*-test or by the Wilcoxon rank sum test. Percentages in the frequency tables of symptoms were based on the total number of patients who had an assessment made and not on the total number of patients treated. *P* values were two-tailed.

Adverse events were summarized by tabulating the number of subjects who experienced each event. Adverse events were categorized using a modified World Health Organization Adverse Reaction table. Where the incidence of events was large enough to be compared between treatments, the comparison was performed using Fisher's exact test.

RESULTS

Patients

Fifty patients were recruited into the study: 26 allocated to balsalazide, 6.75 g/day, and 24 to sulfasalazine, 3 g/

day. Demographic data and disease history are shown in Table 1. The treatment groups were well matched for sex, age and weight. The sulfasalazine group contained more smokers (6/24 vs. 1/26, *P* = 0.045). This was the first attack for 40 of the 50 (80%) patients; the remaining 10 patients had been diagnosed previously, but had not received medical treatment for at least 2 months prior to the study. Of the six patients who had suffered from relapses in the last 2 years, three were allocated to each group. The extent of disease was well balanced across the treatment groups.

Clinical efficacy

The overall study outcome, including all patients, is shown in Table 2. The most important statistically significant difference between the two treatments was that more patients were withdrawn for adverse events whilst taking sulfasalazine than whilst taking balsalazide (*P* = 0.004). There were trends in favour of balsalazide in respect of the rates of remission and the smaller numbers of patients withdrawn because the treatment was ineffective, but these were not statistically significant.

Two patients (one in each group) were withdrawn from the study because they failed to comply with the protocol: one failed to attend the clinic visits and one

Table 1. Patient characteristics and disease history at entry

	Balsalazide (6.75 g) (<i>n</i> = 26)	Sulfasalazine (3 g) (<i>n</i> = 24)
Sex (male/female)	17/9	16/8
Age (years)		
Mean (\pm s.d.)	46 (\pm 14.9)	43 (\pm 18.3)
Range	21–69	21–81
Weight (kg)		
Mean (\pm s.d.)	71.8 (\pm 13.4)	72.7 (\pm 12.4)
Smoker (yes/no)	1/25	6/18
Duration of disease (years)		
Mean (\pm s.d.)	1.5 (\pm 3.4)	1.5 (\pm 2.4)
First attack (yes/no)	23/3	17/6
Extent of disease		
Extensive	3	3
Left-sided	8	5
Proctosigmoiditis	10	11
Not known	5	5
Previous treatment		
With sulfasalazine (yes/no)	2/24	1/23
With mesalazine (yes/no)	0/26	0/24

	Balsalazide (6.75 g)		Sulfasalazine (3 g)	
	<i>n</i>	(%)	<i>n</i>	(%)
Completed study, in clinical and sigmoidoscopic remission	13	(50)	9	(38)
Completed study, not in remission	8†	(31)	2†	(8)
Withdrawn, treatment ineffective	2	(7.5)	3	(12)
Withdrawn, protocol violation	2	(7.5)	1	(4)
Withdrawn, adverse event	1*	(4)	9*	(38)
Total	26	(100)	24	(100)

* $P = 0.004$, chi-squared test.

† $P = 0.077$, chi-squared test.

took only one capsule (instead of three) three times daily. A further patient in the balsalazide group was withdrawn at 2 weeks when it was realized that he had been taking sulfasalazine, 3 g daily, at the time of study entry.

One patient in the balsalazide group and nine in the sulfasalazine group withdrew from the study because of adverse events. Summary information on these patients is given in Table 3. None of the patients withdrawn for adverse events had received any previous exposure to 5-aminosalicylic acid therapy.

Symptoms of general well-being, bowel frequency and stool blood were assessed at each visit and pulse rate and weight were monitored. There was no clinically significant change in pulse rate over the study. Weight gain from entry to 8 weeks was seen in both groups: the mean increase in the balsalazide group ($n = 21$) was

1.2 kg, and in the sulfasalazine group ($n = 11$) was 0.4 kg, but the difference between the groups was not significant ($P > 0.2$).

Well-being was measured at each visit on a four-point scale ranging from normal to unable to work. The proportion of patients with normal well-being increased at each visit for both treatment groups. In the balsalazide group, 19 patients (86%) had normal well-being at 8 weeks. In the sulfasalazine group, seven patients (58%) reported this grade ($P = 0.18$). The majority of the patients had their well-being at least impaired at entry, although there were slightly more patients with normal well-being at entry in the balsalazide group compared to the sulfasalazine group ($P > 0.2$).

Bowel frequency was measured on a three-point scale (0, 0–2 bowel actions per day; 1, 3–5 bowel actions per

Table 2. Study outcome

Table 3. Patient withdrawals because of adverse effects (NK, not known)

Drug	Day of onset	Day of withdrawal	Type of event	Comment or outcome
Balsalazide	4	5	Swollen face, itchy erythematous rash on neck	Recurred on rechallenge with sulfasalazine. Recovered
Sulfasalazine	10	13	Very severe headache, nausea, abdominal pain and lethargy	Steroids and mesalazine started
Sulfasalazine	NK	19	Carcinoma of lung diagnosed	Not drug related. Treated and alive 4 years later
Sulfasalazine	9	11	Acute pancreatitis	Treated conservatively and recovered
Sulfasalazine	6	15	Intense nausea	Events arising after full dosage achieved
Sulfasalazine	6	15	Severe nausea, severe headache and depression	Events stated to be intolerable
Sulfasalazine	6	15	Severe headache, severe dizziness	Treatment stopped day 7
Sulfasalazine	< 11	17	Rash, headache	Treatment stopped day 11
Sulfasalazine	1	8	Severe headache, nausea, depression, light-headed	Olsalazine started
Sulfasalazine	15	21	Headaches	Treatment stopped day 20

day; 2, more than 6 bowel actions per day). The proportion of patients with a bowel frequency of between 0 and 2 per day increased during the study for both treatments. The change in bowel frequency from entry to 8 weeks is shown in Table 4. Improvement in the balsalazide treatment group was significant at 2 weeks ($P = 0.011$), 4 weeks ($P = 0.011$) and at the end of treatment ($P < 0.001$), whilst, in the sulfasalazine group, it was not significant until week 4 ($P = 0.03$), indicating a faster improvement for balsalazide.

Rectal bleeding was assessed on a three-point scale at each clinic visit, ranging from absent to more than a trace. The number of patients with no blood in their stools increased at each clinic visit for the balsalazide group, and increased at 2 weeks but then decreased slightly in the sulfasalazine group. The changes in rectal bleeding from entry to 8 weeks are summarized in Table 5.

Rigid sigmoidoscopy was performed at entry, 4 weeks and at the final visit. The results were graded on a four-point scale, ranging from normal to spontaneous bleeding, and are shown in Table 6. The proportion of patients with normal sigmoidoscopic appearance increased at each visit for both treatments. However, the difference between the treatment groups was not statistically significant.

Rectal biopsies were performed at entry and at the final visit. All the slides from these biopsies were reviewed by one consultant histopathologist, who was blind to the

study treatment, and who graded each biopsy on a four-point scale from normal to severe inflammation. These grades were assigned retrospectively after each patient had finished the study. Two biopsies failed to yield suitable tissue. Table 7 shows the frequency of patients in each of the four categories of inflammation for each treatment group. All but one of the patients had at least mild inflammation at entry, with 28 of 48 (58%) having severe inflammation. Some improvement in the histological grades can be seen on the final assessment, but only 11 of 32 (34%) patients had no inflammation. Both treatments showed similar histological improvements among patients tolerating treatment.

Patient diaries

On a daily basis, patients recorded in their diaries the consistency of their stools and whether blood and mucus were passed. Three patients (two in the sulfasalazine group and one in the balsalazide group) did not return their diaries. The diary data were analysed for 3-day periods at baseline, week 4 and at the end of treatment. The median number of loose stools was reduced from eight at baseline in both groups to one for the balsalazide group and none for the sulfasalazine group at week 8. The median number of stools with blood and mucus at baseline was four for the balsalazide group and five for the sulfasalazine group. These medians reduced to zero for the balsalazide group at 4 weeks and for both the balsalazide and the sulfasal-

Table 4. Change in bowel frequency score from entry to 8 weeks

	Balsalazide (6.75 g)		Sulfasalazine (3 g)		Between-treatment analysis
	<i>n</i>	(%)	<i>n</i>	(%)	
Worse	0	(0)	1	(8)	$P > 0.2$
No change	8	(36)	5	(42)	
Improved	14	(64)	8	(50)	
Within-treatment analysis	$P < 0.001$		$P = 0.060$		

Table 5. Change in rectal bleeding from entry to 8 weeks

	Balsalazide (6.75 g)		Sulfasalazine (3 g)		Between-treatment analysis
	<i>n</i>	(%)	<i>n</i>	(%)	
Worse	0	(0)	0	(0)	$P > 0.2$
No change	3	(14)	2	(17)	
Improved	19	(86)	10	(83)	
Within-treatment analysis	$P < 0.001$		$P = 0.003$		

Table 6. Summary of sigmoidoscopic appearances (0, normal; 1, mild minimal/no bleeding; 2, contact bleeding; 3, spontaneous bleeding) at each visit

	Score	Balsalazide (6.75 g) (<i>n</i> = 26)		Sulfasalazine (3 g) (<i>n</i> = 24)	
		<i>n</i>	(%)	<i>n</i>	(%)
At entry	0	0	(0)	0	(0)
	1	1	(4)	5	(22)
	2	17	(65)	14	(61)
	3	8	(31)	4	(17)
At 4 weeks	0	3	(14)	1	(7)
	1	12	(57)	11	(79)
	2	4	(19)	2	(14)
	3	2	(10)	0	(0)
At 8 weeks	0	7	(33)	6	(50)
	1	7	(33)	4	(33)
	2	6	(29)	0	(0)
	3	1	(5)	2	(17)

azine groups at 8 weeks. Overall, the diary data showed similar improvements in both groups.

Side-effects

Details of any side-effects were recorded at each clinic visit. Adverse events were also collected in the well-being section, final evaluation page and the patient's diary card. Three patients experienced adverse events categorized as serious by virtue of causing hospital admission. One patient in the balsalazide group suffered from an erythematous rash on the neck on day 5 of treatment in response to the study medication and required a brief admission. This patient subsequently developed a rash

with sulfasalazine and aspirin. One patient on sulfasalazine presented with chest pain on day 8 of the study and was found to have a venous thrombosis in the leg and carcinoma of the lung. Another patient on sulfasalazine was admitted to hospital on day 11 with acute pancreatitis which settled with conservative medical treatment. All patients had their study medication stopped at the time of the serious adverse events and were withdrawn from the study.

As noted above, adverse events caused the withdrawal of 10 patients overall (nine on sulfasalazine and one on balsalazide) ($P = 0.004$), of which three were defined as serious. A review of the incidence of adverse events showed that at least one non-serious adverse event was experienced by 17 of 26 (65%) patients in the balsalazide group and 21 of 24 (88%) patients in the sulfasalazine group ($P = 0.10$). Many of these were mild aches and non-specific fatigue, and were balanced between the treatment groups. For three adverse events, there was an imbalance between the groups in favour of balsalazide. Headache was the most common side-effect seen in this patient population, with an incidence of 5/26 (19%) in the balsalazide group and 13/24 (54%) in the sulfasalazine group ($P = 0.018$). Gastrointestinal events, including abdominal pain and dyspepsia, were evenly balanced between the groups; however, there was an advantage for balsalazide with respect to nausea (2/26 (8%) vs. 8/24 (33%), $P = 0.035$) and vomiting (0/26 vs. 4/24, $P = 0.030$).

Laboratory data

There were no significant changes in any of the haematological or biochemical tests performed at entry

	Score	Balsalazide (6.75 g) (<i>n</i> = 26)		Sulfasalazine (3 g) (<i>n</i> = 24)	
		<i>n</i>	(%)	<i>n</i>	(%)
At entry	0	1	(4)	0	(0)
	1	0	(0)	1	(5)
	2	10	(38)	8	(36)
	3	15	(58)	13	(59)
	Median score	3		3	
At 8 weeks (or final)	0	6	(30)	5	(42)
	1	5	(25)	2	(17)
	2	5	(25)	3	(25)
	3	4	(20)	2	(17)
	Median score	1		1	

Table 7. Summary of histological grades (0, normal; 1, minimal inflammation but not active disease; 2, moderate inflammation; 3, severe inflammation)

and at the end of the study period. In six of the 26 patients in the balsalazide group, the erythrocyte sedimentation rate fell from high to normal, as it did in three of the 24 patients in the sulfasalazine group. Three patients in each group showed a change from high to normal platelet counts. There was no significant change in the urinalysis results from either patient group.

DISCUSSION

In this small study of the initial management of patients with active ulcerative colitis of mild to moderate severity, balsalazide, 6.75 g, proved to be significantly better tolerated than sulfasalazine, 3 g.

Sulfasalazine has been in use for many years for the treatment of ulcerative colitis and was included in this trial as an active control. The dose of 3 g daily for the sulfasalazine group was chosen because of previous clinical experience, which confirmed published evidence,²¹ indicating that the use of a dose higher than 3 g was likely to be so poorly tolerated that no comparison of efficacy would be possible.

In terms of patient tolerability, the results from this study indicate a marked difference in favour of the newer compound, balsalazide. Of the 26 patients on balsalazide, one withdrew because of an adverse event, whilst nine of 24 on sulfasalazine withdrew for the same reason ($P = 0.004$). All except one (on sulfasalazine) of these adverse events were thought by the investigators to be related to the trial drug. Of the more common adverse events which did not lead to withdrawal, significantly fewer patients in the balsalazide group were recorded as suffering from headaches, nausea or vomiting, whilst abdominal pain and dyspepsia were evenly divided. The finding of the better tolerability of balsalazide compared to sulfasalazine has also been observed in another study of balsalazide vs. sulfasalazine, in which oral and topical steroids were also used,¹⁹ and in a maintenance study of balsalazide and sulfasalazine.¹⁶

The difference in the proportion of patients able to complete the trial may confound estimates of efficacy; however, the method of analysis is conservative to account for this. No difference emerged in the proportion of patients obtaining remission in the acute attack (about 60% in each group) among patients able to tolerate treatment. The grading and measurement of symptoms and signs were consistent with the clinical improvement in both groups. There were,

however, some interesting if minor differences between the groups. The degree of weight gain was slightly higher for the balsalazide group. Changes in sigmoidoscopic grade and bowel frequency scores, while showing no statistically significant differences between the groups, showed trends supporting a better result with balsalazide.

The inclusion of histology in the assessment of efficacy was intended to identify patients in whom clinical remission was also associated with histological remission. The number of patients in categories 1 and 2 (normal and minimal inflammation without active disease) increased in both treatment groups, from one patient in each group to 11 for balsalazide and seven for sulfasalazine. In both groups, this represents over half the patients completing the study. Histological improvement is known to lag behind the clinical response, and the changes observed are compatible with the clinical response.²²

In the planning of this trial, it had been hoped that using double doses of available 5-aminosalicylic acid (mesalazine) in the balsalazide group would lead to improved efficacy. The dose-response curve for mesalazine, however, has been found to be flat with other delivery systems,²³ although a recent report has suggested that doses of oral mesalazine up to 4 g may be beneficial.²⁴ The doses of sulfasalazine and balsalazide given in this trial are equivalent to the doses of mesalazine known to be clinically effective, but at the lower end of the therapeutic range. The patient numbers for comparison of the two active treatments are low. The marginal differences in symptomatic findings may reflect a possible dose-response relationship with mesalazine released by azoreductase into the colon.

The treatment groups were generally well matched, but there were more smokers in the sulfasalazine group (6/24 vs. 1/26, $P = 0.045$). It is unlikely that this had any impact on the result of the trial, particularly as smokers have a better outcome than non-smokers,²⁵ and nicotine patches have been reported as beneficial in active ulcerative colitis.²⁶

This study is unusual in two respects. Firstly, patients were selected who had previously received no treatment; because of this, most patients were in their initial attack of ulcerative colitis. This allowed the inclusion of patients who had no previous experience of sulfasalazine, thus eliminating an important bias seen in other studies of sulfasalazine vs. the newer 5-aminosalicylic

acid-releasing agents, where patients intolerant of sulfasalazine have been excluded.^{4, 27} Secondly, patients were treated with oral 5-aminosalicylic acid-releasing medication only; no rescue medication was allowed, including the use of rectal preparations and corticosteroids. The conclusion of the study, that sole treatment with balsalazide, 6.75 g, is an effective and safe treatment for mild to moderate active ulcerative colitis, may not be applicable to other situations, for example, where patients are already on maintenance 5-aminosalicylic acid treatment or where corticosteroids are co-administered. The study does not directly address the question of whether patients with mild to moderate ulcerative colitis should be prescribed corticosteroids at the onset of their initial attack. Only a direct comparison of corticosteroids with balsalazide can answer this, but this study would certainly support the withholding of corticosteroids in patients without systemic upset until the initial treatment with balsalazide has been explored. The only studies in the literature to address the question of whether 5-aminosalicylic acid-releasing treatment or corticosteroids are required used sulfasalazine, and were subject to the same poor tolerability as seen in this study.^{1, 28}

The delivery system, via the colonic bacterial azoreductase, is not the subject of this study as both active treatments employed this mechanism; the differences between the treatments involved the toxicity of the carrier molecule and the dose of 5-aminosalicylic acid delivered. Other studies have compared the azo-bond reductase delivery system with pH-dependent release and time-dependent release in the setting of mild to moderate colitis.^{13–15} Although the designs of these studies were different, when considered with the results of this study, it can be concluded that sulfasalazine is insufficiently tolerated to be the drug of choice and pH-dependent release mesalazine (Asacol) may be less reliably delivered to the diseased colon than balsalazide, which consistently appears to be effective and well tolerated.

Balsalazide is a relatively new drug compared to sulfasalazine, and is therefore more expensive at current prices. From the data presented here, the difference in cost of around £77 (UK prices £100 vs. £23) over 8 weeks is offset by the superior tolerability, with intolerance reduced from 38% to 4%. The choice of a well-tolerated therapy is especially important for initial treatment, as successful first-line therapy will prevent the loss of confidence and escalation to more toxic second-line agents.

In conclusion, in this double-blind study, balsalazide, 6.75 g, was significantly better tolerated than sulfasalazine, 3 g, in the initial treatment of patients with active ulcerative colitis of mild to moderate severity. The results support the use of balsalazide as the sole treatment of initial attacks of this condition.

ACKNOWLEDGEMENTS

The help of Dr D. J. Dawson and Professor M. G. Bramble is gratefully acknowledged. We are also indebted to the patients and nursing staff involved.

The study was initially sponsored by Biorex Laboratories Ltd.

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